CLINICAL PROTOCOL

A RANDOMIZED CONTROLLED EXAMINER-BLIND PHASE II PROOF-OF-PRINCIPLE CLINICAL STUDY INVESTIGATING THE EFFICACY OF AN EXPERIMENTAL DENTIFRICE CONTAINING SODIUM BICARBONATE, HIGH MOLECULAR WEIGHT SODIUM HYALURONATE AND SODIUM FLUORIDE ON GINGIVITIS AND PLAQUE REMOVAL IN A POPULATION WITH MILD-MODERATE PLAQUE-INDUCED GINGIVITIS

Protocol Number:	**208175**
Compound/Product Name:	Experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w high molecular weight sodium hyaluronate and 0.221% w/w sodium fluoride
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	• Addition of Health Canada CTA submission no. to the title page. • Addition of NPN no. for washout product and NPN no. for negative control product. • Update to inclusion criteria: a female subject of childbearing potential must have negative pregnancy test results at screening and baseline. • Corrected wording of reference to section 5.5.4 in the inclusion criteria. • Update to exclusion criteria to include: a subject with any other clinical serious or unstable conditions (e.g. cardiovascular diseases, diabetes, liver disorders and kidney disorders) which may affect study outcomes and/or subject safety. • Update to exclusion criteria to include: a subject with a bleeding disorder that may affect study outcomes and/or subject safety. • Addition of threshold of compliance with allocated study treatment. • Clarifying that statistical comparisons under secondary analyses are pairwise.
Amendment 2	3.0	• Section 5.5.4 updated to clarify time period that intrauterine device or barrier method of contraception should be in place prior to study participation. Clarity of acceptability of male partner sterilization ≥3 months prior to study participation, or documentation of a 0 sperm count. • Section 13.3 updated to clarify that clinical study site personnel involved in providing subject care, or conduct of any of the dental assessments will not be responsible for obtaining written informed consent.
Amendment 3	4.0	• Wash-out period amended to 10 to 28 days in the following sections: Study Design section of the Protocol Summary, Table 1-1, Sections 4.1, 4.2 and 8.2.1.

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	BDS
Investigator Signature:	
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

Background and Rationale

GlaxoSmithKline Consumer Healthcare (GSKCH) has developed an experimental dentifrice containing 67% weight for weight (w/w) sodium bicarbonate, 0.2% w/w high molecular weight (HMW) sodium hyaluronate and 0.221% w/w sodium fluoride for the treatment of gingivitis and plaque accumulation. This follows published literature evidence of 0.2% w/w HMW sodium hyaluronate in a gel format demonstrating efficacy in the treatment of gingivitis when used as an adjunct to regular toothbrushing. Given that there are currently no published clinical data investigating the efficacy of sodium hyaluronate (hyaluronic acid, HA) in a toothpaste for the treatment of gingivitis, a Proof-of-Principle (PoP) clinical study is required to explore the inclusion of HMW sodium hyaluronate in a twice-daily use sodium bicarbonate/ sodium fluoride toothpaste. This PoP study will investigate the efficacy of an experimental dentifrice containing 0.2% w/w HMW sodium hyaluronate in a twice daily use 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride toothpaste compared to a regular fluoride dentifrice, and also whether this provides any additional benefit in reducing gingival inflammation/ bleeding compared with a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride containing toothpaste.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
Secondary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.

Exploratory	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), over 2 weeks' twice daily use.	No. of bleeding sites at 3 days, 1 and 2 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), over 6 weeks' twice daily use.	Mean BI at 3 days, 1, 2 and 6 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by Modified Gingival Index (MGI), over 6 weeks twice daily use.	Mean MGI at 3 days, 1, 2 and 6 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of plaque accumulation, as measured by a Plaque Index (TPI; overall and interproximal), over 6 weeks twice daily use.	Mean TPI (overall and interproximal) at 3 days, 1, 2 and 6 weeks.
To evaluate and compare MGI and mean BI in low (<45 bleeding sites) and high (≥45 bleeding sites) BI subgroups following twice daily use of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice and a fluoride control dentifrice, over 6 weeks twice daily use.	Mean MGI and mean BI at 3 days, 1, 2 and 6 weeks within each subgroup (low and high number of bleeding sites)

Safety	
To assess the oral tolerability of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, and a fluoride control dentifrice over 6 weeks twice daily use.	Treatment-emergent adverse events over 6 weeks.

Study Design

This will be a single center, controlled, single blind (examiner blind), randomized, stratified (gender and baseline number of bleeding sites) three-treatment arm, parallel design, clinical study. Study subjects will be aged 18-65 years, non-smokers, in good general health with generalized mild-moderate plaque-induced gingivitis and ≥ 20 natural teeth that meet all study criteria at both the Screening and Baseline visits (including ≥ 40 evaluable surfaces for MGI, BI, and TPI).

Approximately 120 (n=40/group) subjects will be randomized to one of the study products.

This study will consist of 6 study visits. At Visit 1, Screening, after signing informed consent, subjects will undergo an Oral Soft Tissue (OST) examination, an Oral Hard Tissue (OHT) examination and a gross assessment of gingival health, in addition to the standard (inclusion, exclusion, medical history, demographics, prior/current medications) procedures to assess eligibility for the study. Subjects will return to site 10-28 days after the Screening Visit, for Visit 2, Baseline.

At the Baseline Visit, subjects will undergo, in the following order, a full OST/ OHT examination followed by assessments of gingival inflammation (MGI), gingival bleeding (BI) and supra-gingival plaque using the Turesky Plaque Index (TPI). Eligible subjects will be stratified based on gender and baseline number of bleeding sites (Low: < 45/ High ≥ 45 bleeding sites), to ensure a balance of gingivitis across both treatment groups and then randomized to study product.

Subjects with mean MGI or TPI scores outside the study range will be discontinued from the study at this visit. To control inter-examiner variability, the same examiner will be used throughout the study for all clinical assessments (MGI, TPI, BI).

All randomized subjects will then receive a full mouth dental prophylaxis (followed by flossing) to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. All subjects will enter the treatment period with no visible plaque (TPI=0).

After all clinical assessments, subjects will be instructed to brush for 1 timed minute, in their usual manner, with their assigned study product and then instructed to continue using their assigned product twice daily (morning and evening), after which they will return to site for their Day 3 (Visit 3) assessments. Subjects will then continue using their assigned dentifrice for 1 and 2 weeks (Visits 4 and 5), after which they will return for their Week 6 (Visit 6) assessments. Subjects will continue to record all brushing events in the diary provided, and this will be reviewed by the site at each study visit.

After the Week 6 visit, study closeout procedures (return of study product etc.) will take place and the subject may undergo an additional prophylaxis if it is deemed necessary by the examiner.

Safety and oral tolerability of the study products will be monitored over the 6-week treatment period by review of reported Adverse Events and Incidents.

Study Investigational Products

	Experimental Product	Positive control	Negative control
Treatment Description	Dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w sodium hyaluronate and 0.221% w/w sodium fluoride	Dentifrice containing 67% w/w sodium bicarbonate and 0.221% w/w sodium fluoride	Dentifrice containing 1100ppm fluoride as sodium fluoride
Product Name	Experimental dentifrice CCI [redacted]	Registered as a Non-prescription Natural Health Product (NNHP) in Canada CCI [redacted] (NPN no. CCI [redacted])	Crest Cavity Protection (Canadian marketplace) (NPN CCI [redacted])

Type and Planned Number of Subjects

Sufficient subjects (meeting the inclusion/ exclusion criteria) will be screened (approximately 160 subjects) to randomize 120 subjects (40 per treatment group) to ensure 108 evaluable subjects (36 evaluable subjects per group) complete the week 6 assessment (thus allowing for a 10% drop-out rate).

Statistical Analyses

The primary efficacy variable is the number of bleeding sites at 6 weeks. Number of bleeding sites will be calculated as the number of sites with a bleeding index score of 1 or 2.

The number of bleeding sites at 6 weeks will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and gender as factors and baseline number of bleeding sites as covariate.

Adjusted means and treatment differences between the 67% w/w sodium bicarbonate & 0.2% w/w HMW sodium hyaluronate and the fluoride control dentifrice will be provided along with 95% confidence intervals.

1.1 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening		Study Period				
	Visit 1 (-28 to -10 days)	Washout Period: minimum 10 Days/ maximum 28 days	Visit 2 Day 0[1] Baseline	Visit 3 Day 3+1 days[1]	Visit 4 Day 7±2 (Week 1)[1]	Visit 5 Day 14±2 (Week 2)[1]	Visit 6 Day 42±3 (Week 6)[1]
Informed consent	X						
Demographics	X						
Medical History	X						
Prior/ current medications and treatments	X		X				
Oral soft tissue (OST) examination	X		X	X	X	X	X
Oral hard tissue (OHT) examination	X		X				X
Gross gingival assessment[2]	X						
Urine pregnancy test[7]	X		X				
Inclusion/ Exclusion Criteria	X		X				
Subject Eligibility	X		X				
Subject Continuance				X	X	X	X
Dispense washout dentifrice, toothbrush, diary & timer	X						
Oral hygiene instruction & supervised brushing with washout dentifrice	X						
Return washout products/ compliance checks			X				
Concomitant medications & treatments			X	X	X	X	X
Modified Gingival Index (MGI) assessment[3]			X	X	X	X	X
MGI repeat assessment[3]			X	X	X	X	X
Bleeding Index (BI) assessment			X	X	X	X	X
Plaque disclosure & Plaque Index (TPI) assessments			X	X	X	X	X
TPI repeat assessment[3]			X	X	X	X	X

Stratification/randomization			X				
Sub- & supra-gingival prophylaxis with 2nd examiner to confirm TPI=0 via plaque disclosure			X				
Dispense study products[4]			X				
Collect study products, assess compliance and return to subject				X	X	X	
Oral hygiene instruction & supervised brushing with study product at site			X	X	X	X	
Return all study products to site							X
End of study dental prophylaxis (optional)[5]							X
Adverse Events/ Incidents[8]	X		X	X	X	X	X
Study Conclusion							X

Abbreviations: OST = Oral Soft Tissue; OHT = Oral Hard Tissue; MGI = Modified Gingival Index; BI = Bleeding Index; TPI = Turesky Plaque Index

Footnotes:

1. Subjects will abstain from overnight toothbrushing for a minimum of 12hrs (+6hr, -2hr) immediately prior to the assessment visits (Visits 2, 3, 4, 5 and 6)
2. In relation to the general dentition inclusion/ exclusion criteria
3. At least 2 repeatability assessments should be performed each day (≥ 1 in the morning; ≥ 1 in the afternoon)
4. Study products include study dentifrice, toothbrush, study instructions, diary & timer. Subjects will be instructed to bring all supplies to site at subsequent visits to determine treatment compliance, prior to being returned to the subject.
5. Prophylaxis will be offered to subjects who are deemed to require it in the opinion of the investigator/ examiner after all efficacy measures have been completed. This will be documented in the CRF.
7. Female subjects of child bearing potential only
8. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs), and Incidents will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

2 INTRODUCTION

Gingivitis is a reversible inflammatory response to the presence of dental plaque (CCI), which typically presents as redness, swelling (oedema) and/ or bleeding of the gums at the gingival margin surrounding the tooth. Gingivitis is a reversible condition but, if left untreated, can progress to the irreversible phase of periodontitis, where inflammation extends to the underlying tissues, periodontal ligament and alveolar bone. The resulting loss of these structures can eventually lead to tooth loss through destruction of the periodontal tissues supporting the tooth (CCI). Periodontitis is reported to affect 5-20% of the world's population CCI). The maintenance of good gingival health is therefore important in preventing gingivitis and the development of periodontal disease (CCI).

Dental plaque is a soft, sticky, colourless deposit of bacteria which collects on teeth and along the gingival margin; it is the causative agent of gingivitis and periodontitis (CCI . Gingivitis develops when plaque elicits a local inflammatory response in the gingivae at the site of its accumulation (CCI . Gingivitis is prevented and resolved through effective plaque control, primarily via mechanical plaque removal (i.e. toothbrushing) (CCI).

Many people are unable to achieve adequate plaque control by toothbrushing alone. The effect of toothbrushing can be augmented by the use of a dentifrice CCI) and antimicrobial ingredients. Antimicrobial agents (such as metal salts, cetylpyridinium chloride and chlorhexidine) have been included in daily use dentifrice and mouth rinse formulations for many years, with a view to delivering improved plaque control and gum health benefits (CCI). They complement mechanical plaque removal by inhibiting the growth of bacteria (via bacteriostatic and/or bactericidal activity) in areas of the mouth less accessible to the toothbrush and by interfering with the re-colonisation of plaque bacteria (CCI).

GSKCH markets a sodium bicarbonate dentifrice (67% w/w; parodontax) for the treatment of gingivitis. This is supported by a large body of evidence demonstrating its efficacy against gingivitis. Specifically, two clinical studies conducted in the US investigated bleeding (bleeding index [BI]), gingival inflammation (modified gingival index [MGI]) and plaque (plaque index [TPI]) outcome measures after 24 weeks in duration, with twice daily use (GSKCH Clinical Study RH02433/ 202192, 2017; CCI).

There are currently no published clinical data investigating the application of HMW sodium hyaluronate in a toothpaste for the treatment of gingivitis. A Proof-of-Principle (PoP) clinical study is therefore being conducted to explore the inclusion of sodium hyaluronate in a twice-daily use toothpaste. This will provide data to help understand whether HMW sodium hyaluronate in a twice daily use 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride toothpaste provides additional benefit in reducing gingival inflammation/ bleeding compared with a regular fluoride dentifrice, along with comparing to a toothpaste containing 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride.

2.1 Study Rationale

There are currently no published clinical data investigating the efficacy of HMW sodium hyaluronate (hyaluronic acid, HA) in a toothpaste for the treatment of gingivitis. A PoP clinical study is therefore required to explore the inclusion of HMW sodium hyaluronate in a twice-daily use sodium bicarbonate toothpaste. This will provide data to help understand whether 0.2% w/w HMW sodium hyaluronate in a twice daily use 67% w/w sodium bicarbonate/ 0.221% w/w toothpaste provides any benefit in reducing gingival inflammation/ bleeding compared with a regular fluoride dentifrice, and whether it provides any additional benefit compared to a 67% w/w sodium bicarbonate/ 0.221% w/w containing dentifrice. The rationale for inclusion of 0.2% w/w HMW sodium hyaluronate relates to evidence of 0.2% w/w HMW sodium hyaluronate gel demonstrating efficacy in the treatment of gingivitis when used as an adjunct to regular toothbrushing ([redacted]).

The aim of this proof of principle clinical study is to evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride to control gingivitis (gingival bleeding and visual signs of gingival inflammation) in healthy adult volunteers with generalized mild to moderate gingivitis over 6 weeks' use through twice daily toothbrushing.

Several clinical studies evaluated the anti-gingivitis efficacy of a sodium bicarbonate dentifrice in the scientific literature. These studies range from 4 weeks to 6 months use ([redacted]) along with a plaque re-growth model over 4-days ([redacted]). Taken together, GSKCH sponsored, and externally published studies demonstrate efficacy of sodium bicarbonate containing dentifrice against measures of gingivitis, along with a favorable safety profile.

There are currently no known clinical studies, conducted either within GSKCH or external published studies, investigating the effect of HMW sodium hyaluronate within a dentifrice in relation to oral health benefits. Given this lack of data for a dentifrice format, several published studies on other formats such as gels or sprays, have been identified, and including 2 systematic reviews which conclude that the majority of clinical studies describe a positive beneficial, occasionally statistically significant, effect of HMW sodium hyaluronate on gingival health ([redacted]). Several clinical studies investigate the anti-gingivitis efficacy of sodium hyaluronate ([redacted]) All reported reductions in gingivitis (gingival bleeding and/ or gingival inflammation) for the sodium hyaluronate treatment, compared to placebo/ control treatments; some also reported reductions in supra-gingival plaque and gingival crevicular fluid (GCF) volume/ composition.

Complete information for the experimental 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

2.2 Background

parodontax is a specialist gum health toothpaste that contains high levels of sodium bicarbonate (62-67% w/w) to facilitate removal of plaque bacteria thereby reducing gingivitis and has a large body of evidence in support of anti-gingivitis and plaque removal efficacy. This PoP study investigates the inclusion of 0.2% w/w HMW sodium hyaluronate to the 67% sodium bicarbonate dentifrice formulation for use as a twice daily use dentifrice; the aim to develop a daily use toothpaste containing sodium hyaluronate with the intention of providing improved/ fast gum healing.

Sodium hyaluronate is a naturally occurring polysaccharide (glycosaminoglycan) which plays a role in the function of extracellular matrices, including those of mineralized and non-mineralised periodontal tissues. It is a critical component of the extracellular matrix and contributes significantly to tissue hydrodynamics, cell migration and reduced proliferation and, at low (rather than high) molecular weight, plays a potentially important anti-inflammatory role through the inhibition of tissue destruction and facilitated healing. The use of sodium hyaluronate is already established in orthopaedics, dermatology and ophthalmology.

A limited number of studies have reported the efficacy of HMW sodium hyaluronate in the oral environment (in gel, mouthwash and spray forms) for the treatment of gingivitis, with most available evidence based on the gel format (0.2% w/w HMW sodium hyaluronate) when used as an adjunct to regular toothbrushing. To date, there are currently no clinical data supporting the application of sodium hyaluronate in a daily use toothpaste for the treatment of gingivitis.

Since there are currently no published clinical data investigating the application of HMW sodium hyaluronate in a toothpaste for the treatment of gingivitis, a PoP clinical study is required to explore the inclusion of HMW sodium hyaluronate in a twice-daily use toothpaste. This will provide data to help understand whether HMW sodium hyaluronate in a twice daily use 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride toothpaste provides any benefit in reducing gingival inflammation/ bleeding compared with a regular fluoride dentifrice along with whether there is any additional benefit compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice (i.e. without inclusion of sodium hyaluronate).

The main aim of the current PoP study is to investigate the efficacy profile of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a regular fluoride negative control dentifrice, for gingival bleeding (primarily assessed by number of bleeding sites), inflammation, and plaque removal, at multiple time points over a 6-week treatment period. In addition, early timepoints will also be investigated (3 days, 1 & 2 weeks for inflammation), relating to published evidence of improved gingival health and plaque accumulation with adjunctive use of sodium hyaluronate, in a gel format, for as little as 3 days.

2.3 Mechanism of Action/Indication

Sodium bicarbonate in a toothpaste has been shown to enhance the removal of plaque biofilms. Some of the proposed modes of action of sodium bicarbonate in toothpaste are;

- The large crystals of sodium bicarbonate may help the toothbrush to physically displace plaque from the tooth surface.

- Sodium bicarbonate may reduce the viscosity of the polysaccharide matrix which helps bind the bacteria together and to the tooth surface, resulting in easier plaque removal.

Sodium hyaluronate (hyaluronic acid, HA) is a naturally occurring polysaccharide (glycosaminoglycan) which plays a role in the function of extracellular matrices, including those of mineralized and non-mineralized periodontal tissues. The sodium hyaluronate under investigation in this project is of high molecular weight (HMW; 2,000,000 Da). For the treatment of gingivitis, its hygroscopic nature helps to provide an improved environment in which the body can naturally heal.

In relation to oral health, a limited number of studies have reported on the efficacy of HMW sodium hyaluronate in the oral environment (in gel, mouthwash and spray forms) in the treatment of gingivitis, with most evidence based on the gel format (0.2% w/w HMW sodium hyaluronate) when used as an adjunct to regular toothbrushing ([redacted]CCI[redacted]

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
Secondary	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
To evaluate the efficacy of a dentifrice containing 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), after 6 weeks' twice daily toothbrushing.	Number (no.) of bleeding sites at 6 weeks.
Exploratory	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium	No. of bleeding sites at 3 days, 1 and 2 weeks.

bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), over 2 weeks' twice daily use.	
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by a Bleeding Index (BI), over 6 weeks' twice daily use.	Mean BI at 3 days, 1, 2 and 6 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of gingivitis, as measured by Modified Gingival Index (MGI), over 6 weeks twice daily use.	Mean MGI at 3 days, 1, 2 and 6 weeks.
To evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride compared to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, with both compared to a fluoride control dentifrice, for the assessment of plaque accumulation, as measured by a Plaque Index (TPI; overall and interproximal), over 6 weeks twice daily use.	Mean TPI (overall and interproximal) at 3 days, 1, 2 and 6 weeks.
To evaluate and compare MGI and mean BI in low (<45 bleeding sites) and high (≥45 bleeding sites) BI subgroups following twice daily use of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice and a fluoride control dentifrice, over 6 weeks twice daily use.	Mean MGI and mean BI at 3 days, 1, 2 and 6 weeks within each subgroup (low and high number of bleeding sites)
Safety	
To assess the oral tolerability of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride, a	Treatment-emergent adverse events over 6 weeks.

67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice, and a fluoride control dentifrice over 6 weeks twice daily use.	

This PoP study will be considered successful if the experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride demonstrates a reduction in the number of bleeding sites compared to a fluoride control dentifrice.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-center, examiner-blind, randomized, stratified, three-treatment, parallel group, clinical study in healthy adult volunteers with mild to moderate gingivitis. There will be six visits to the study site: Screening, Baseline, Day 3 and Weeks 1, 2 and 6. Gingivitis will be assessed using a MGI (CCI [redacted]) and a BI (CCI [redacted]). Plaque will be assessed by the Turesky modification of the Quigley Hein (TPI) (CCI [redacted]). All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed.

Gingivitis and plaque accumulation will be grossly assessed at Screening (Visit 1; in relation to subject screening) and then formally assessed (MGI, BI & TPI) at multiple time points across the 6-week treatment period, for all qualifying teeth at Baseline (Day 0) and then onwards (Days 3, 7, 14 and 42). A single clinical examiner will be responsible for the conduct of the gingivitis and plaque measures for the duration of the study for all subjects.

At the Screening visit (Visit 1), subjects will give their written informed consent to participate in the study. Demographics, medical history and current medications will be recorded, followed by an oral examination, a gingival assessment. This will include an OST and OHT examination, dentition exclusions and a gross gingival assessment. Urine pregnancy testing for all female subjects of reproductive potential will also be performed, to ensure that pregnant females are excluded from the study.

Within 10 to 28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from oral hygiene for 12hrs (+6hr; -2hr) i.e. overnight immediately before the visit). At the Baseline visit, subjects will undergo, in the following order, a full OST and OHT examination and assessments of gingival inflammation (MGI), gingival bleeding (BI) and supra-gingival plaque (TPI). Urine pregnancy testing for all female subjects of reproductive potential will also be performed, to ensure that pregnant females are excluded from the study. Eligible subjects will be stratified based on gender and baseline number of bleeding sites (Low: < 45/High ≥ 45 bleeding sites), to ensure a balance of gingivitis across treatment groups. After the Baseline assessments, a full dental prophylaxis will be performed for each subject using periodontal instruments and a standard polishing dental compound prophylaxis paste followed by flossing by the clinician to remove sub and supra-gingival calculus, stain, plaque and debris from the teeth. Subjects teeth will then be re-disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque remaining will be removed

by the clinician as required and including dental polishing with a standard polishing dental compound, sufficient to bring the subject to zero plaque (i.e. TPI=0). All subjects will enter the treatment period with no visible plaque (TPI=0). Subjects will be randomized to study product and then undergo a supervised brushing, where they will be instructed to brush for 1 timed minute at site with their assigned study product, after which they will be instructed to continue using their product twice daily (morning and evening until their next visit).

After using the study dentifrice for 3 days, 1, 2 and 6 weeks, subjects will return to the study, site (Visits 3, 4, 5 and 6 respectively) with overnight plaque (subjects will abstain from overnight toothbrushing for 12hrs (+6hr; -2hr) immediately before each assessment visit), at approximately the same time of day as the baseline visit. The study dentifrice and the diary will be reviewed to determine treatment compliance. Subjects will have a full OST examination and then undergo, in the following order, MGI, BI and TPI assessments. At Visit 6, subjects will return all study supplies and have a dental prophylaxis if deemed appropriate by the investigator or examiner.

At Visits 2, 3, 4, 5 and 6, repeatability data will be generated for MGI and TPI assessments from replicate examinations on the same subject. Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical session, that is, at least one in the morning and at least one in the afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject. Due to the invasive nature of the BI assessment, it is not feasible to conduct an accurate repeatability assessment for this index.

Adverse events and incidents will be recorded from informed consent and at the end of each study visit.

4.2 Rationale for Study Design

The main aim of this proof-of-principle clinical study is to evaluate the efficacy of an experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride against a reference regular fluoride dentifrice to control gingivitis (gingival bleeding and visual signs of gingival inflammation) in dentally and periodontally healthy adult volunteers with mild-moderate gingivitis over 6 weeks' use.

This design is typical of many studies conducted to evaluate the clinical efficacy of dentifrices in the treatment of gingivitis (CCI [redacted]). Study subjects with a pre-specified level of gingivitis are randomized to study product; efficacy is determined after professional dental cleaning and a period of twice-daily brushing, compared to a control/comparator dentifrice.

Healthy subjects with mild-moderate gingivitis will be included in the study population. The defined level of gingivitis at baseline, will help to minimize the risk of an atypical or potential lack of treatment response for subjects with high levels of gingivitis that may otherwise be managed professionally rather than solely via home use of a twice daily dentifrice. Furthermore, subjects will be stratified based on gender and baseline number of bleeding sites to ensure a balance in treatment groups across gingivitis and gender, and given that gender is a known modifier of the initiation and outcome of conditions relating to gingival health, given that hormonal fluctuations through the female menstrual cycle may also influence response to dental plaque and lead to increased variability in the clinical assessment of gingival health (CCI [redacted]

[redacted]). Stratifying by number of bleeding sites at baseline will also facilitate evaluation of gingivitis in low and high gingivitis (number of bleeding sites) subgroups.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of supra-gingival plaque accumulation. A single clinical examiner will be responsible for the conduct of the gingivitis and plaque accumulation measures (the same examiner being able to conduct all gingivitis/ plaque assessments) for the duration of the study for all subjects, to eliminate the possibility of inter-examiner variability.

To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects throughout the study. Due to the invasive nature of the index, repeatability assessments are not feasible for the BI.

A parallel group design has been selected as most appropriate for this investigation. Anticipated differential changes in clinical variables among treatment groups could lead to carryover effects and an altered oral heath state should a crossover design be employed. The dosage regimen of twice daily use (morning and evening) will be the same for each treatment group and is based on consumer habit and common practice within oral care clinical trials.

The dosage regimen of twice daily treatment (morning and evening) for the washout dentifrice and study products will be the same for all subjects, and is based on widely recommended oral hygiene practice, and typical consumer habit. To facilitate compliance with product usage throughout the study, and to enable staff to confirm correct dosing, a supervised brushing will be performed on site at the end of Visits 1-5; subjects will be required to record each brushing in the diary provided, including the time of last brushing prior to returning for the site assessment visits.

During the washout period for this study (minimum 10 days/ maximum 28 days), eligible subjects will use a marketed, regular fluoride toothpaste and toothbrush (as provided). Use of these products will standardize the study population's oral hygiene regimen prior to the Baseline visit and help familiarize subjects with the dosing/diary completion requirements. It will also serve as a 'washout' from any anti-plaque ingredients contained in the subject's own oral hygiene products and allow the gingivae time to recover prior to Baseline assessment of gingival bleeding (following periodontal probing at Screening).

The choice of time points relates to published anti-gingivitis efficacy for a 67% w/w sodium bicarbonate dentifrice after 6 weeks of twice daily use, along with earlier time points relating to published evidence of improved gingival health with adjunctive use of sodium hyaluronate, in a gel format, for as little as 3 days.

A minimum of 20 permanent gradable teeth is similarly in agreement with GSKCH gingivitis clinical studies and being representative of a minimum of a "shortened dental arch" ([redacted]) equating to anywhere between 20-28 gradable teeth (excluding 3rd molars). With 6 sites examined per tooth for the bleeding index ([redacted]), equating to 120-168 bleeding sites measured, a minimum of 20 bleeding sites at Baseline inclusion criteria also represents a minimum of ~12% bleeding sites which is in agreement with the consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions ([redacted]). Furthermore, the baseline levels of

measures of gingivitis and plaque agree with previous GSKCH gingivitis studies including those investigating a sodium bicarbonate containing dentifrice with mean MGI 1.75-2.30 considered representative of generalised mild-moderate gingivitis.

A dental prophylaxis is included as this is considered industry standard in agreement with FDA guidelines (CCI [redacted]), is in agreement with previous GSKCH gingivitis clinical studies, along with a lack of dental calculus/ staining which could otherwise acts as plaque retentive factors for subjects participating in the clinical study.

The negative control dentifrice (Crest Cavity Protection) and the 6-week upper time point are considered important in relation to being able to compare with previous GSK data with the 67% w/w sodium bicarbonate formulation with 6 weeks as the shortest timepoint (24-week studies; (CCI [redacted])).
The comparison of the experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w HMW sodium hyaluronate and 0.221% w/w sodium fluoride to the negative control has been chosen as the primary objective given that this is the minimum requirement to demonstrate study success in relation to performance in plaque/ gingivitis efficacy. Following this, a comparison between the experimental dentifrice to a 67% w/w sodium bicarbonate/ 0.221% w/w sodium fluoride dentifrice (minus the 0.2% w/w HMW sodium hyaluronate) as a positive control with anti-gingivitis efficacy and allowing comparison in relation to the effect of addition of HMW sodium hyaluronate in the experimental dentifrice formulation, thereby allowing additional benchmarking on performance.

Hormonal changes during pregnancy may affect the response of the gingival tissue to plaque bacteria and could impact the gingivitis efficacy measurements (CCI [redacted]). Therefore, women who are pregnant at screening will be excluded and woman who become pregnant during the course of the study will be discontinued. It should be noted however, that there are no safety concerns with pregnant women using any of the study products. Pregnancy testing will also be undertaken as a precaution, given that there are currently no published clinical data investigating the efficacy of HMW sodium hyaluronate in a toothpaste for the treatment of gingivitis, plus that pregnancy is known to influence periodontal status (CCI [redacted]), and therefore potentially influencing the efficacy measures in this study. Pregnancy testing at both screening and baseline will ensure no pregnant women will receive study product.

The effects of smoking on periodontal health are well documented in the scientific literature. Smoking decreases blood flow within the gingival microvasculature and interferes with neutrophil function, suppressing the inflammatory response to dental plaque and masking the clinical signs of periodontal disease (CCI [redacted]). A 14-day experimental gingivitis model reported much less gingival bleeding in smokers compared to non-smokers, even though plaque levels and the composition of the oral microflora were similar between the two groups (CCI [redacted]). Smokers will therefore be excluded from this investigation of product efficacy for the treatment of plaque-induced gingivitis.

According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blinded as to

the treatment the subject receives, but the products under test must be identical in every way (color, flavor, appearance, packaging). Given it is almost impossible to ensure identical appearance, taste and packaging for the dentifrices evaluated in this oral care study, the level of blindness for this study is described as "examiner blind".

4.3 Justification for Dose

The study products are dentifrices, intended for topical oral use, and will be applied by toothbrushing using a manual toothbrush.

The dosage regimen of twice daily treatment (morning and evening) will be the same for all subjects and is based on widely recommended oral hygiene practice/typical consumer habit. Study subjects will be instructed to brush for at least 1 timed minute with their assigned study dentifrice on each brushing occasion. After 6 weeks (Day 42±3 days) twice daily treatment, each subject should complete between approximately 84-90 treatment applications.

Each subject will complete a supervised brushing with their assigned study dentifrice at the end of each study visit (while still at the study site) to enable staff to check correct dosing and encourage compliance with product usage throughout the study.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of this study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last subject in the trial.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Sufficient subjects will be screened (approximately 160 subjects) to randomize 120 to ensure 108 evaluable subjects complete the entire study.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorized representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

Subject eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 to 65 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant/relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. A female subject of childbearing potential must have negative pregnancy test results at screening and baseline.
6. A female subject of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 5 days after the last dose of assigned treatment. A female subject who is of childbearing potential must meet requirements in Section 5.5.4.
7. **AT SCREENING (Visit 1):**
   a. A subject with at least 20 natural, permanent teeth.
   b. A subject with at least 40 evaluable surfaces for MGI, BI and TPI.

      An evaluable surface is defined as having 2/3^{rds} of the natural tooth surface gradable for the selected clinical indices. The following should not be included in the evaluable surface count- third molars; fully crowned/extensively restored, grossly carious, orthodontically banded/bonded or abutment teeth; surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the baseline assessments of the selected clinical indices.

   c. A subject with generalized mild- moderate plaque-induced gingivitis, in the opinion of the clinical examiner, as confirmed by a gross visual examination at the Screening Visit.
8. **AT BASELINE – Prior to Dental Prophylaxis (Visit 2):**
   a. A subject with ongoing hard tissue eligibility and, in the opinion of the clinical examiner, at least 40 evaluable surfaces.
   b. A subject with mean whole mouth MGI between 1.75 and 2.30.
   c. A subject with mean whole mouth TPI score ≥1.5.
   d. A subject with a minimum of 20 bleeding sites.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSKCH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject with any other clinical serious or unstable conditions (e.g. cardiovascular diseases, diabetes, liver disorders and kidney disorders) which may affect study outcomes and/ or subject safety.
5. A subject who is a pregnant female (including a woman who has a positive urine pregnancy test; pregnancy testing will be carried out for all female subjects who are of child bearing potential) or is intending to become pregnant over the duration of the study.
6. A subject who is a breastfeeding female.
7. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
8. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
9. Subject who is a current smoker or an ex- smoker who stopped within 6 months of Screening.
10. Subject who currently uses smokeless forms of tobacco (e.g. chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).
11. A subject with diagnosed xerostomia or taking any medication that in the view of the investigator causes xerostomia.
12. A subject with a medical condition which may directly influence gingival bleeding.
13. A subject with a bleeding disorder that may affect study outcomes and/ or subject safety.
14. Recent history (within the last year) of alcohol or other substance abuse.
15. A subject with a severe oral condition (e.g. acute necrotizing ulcerative gingivitis or oral or peri-oral ulceration including herpetic lesions) that would, in the opinion of the investigator, compromise study outcomes or the oral health of the subject/ examiner if they were to participate in the study.
16. Presence of a tongue or lip piercing, or any other oral feature that could interfere with the usage of a toothbrush.
17. **Medication Exclusions**
    AT SCREENING (Visit 1):

a. A subject currently taking antibiotics or requiring antibiotic use prior to dental prophylaxis or other dental procedures.
b. A subject currently taking an anti-inflammatory medication which, in the opinion of the Investigator, could affect gingival condition.
c. A subject currently taking a systemic medication (e.g. anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g. ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).

18. Medication exclusions

AT BASELINE (Visit 2):

a. A subject who has taken (in the previous 14 days), any antibiotics.
b. A subject who has taken (in the previous 14 days) a systemic medication (e.g. anti-inflammatory, anti-coagulant, immunosuppressants) or traditional/ herbal remedy which, in the opinion of the Investigator, could affect plaque/ gingival condition (e.g. ibuprofen, aspirin, warfarin, cyclosporin, phenytoin, calcium channel blockers).
c. A subject who has used an antibacterial dentifrice or mouthwash (e.g. chlorhexidine) or any oral care product that in the view of the investigator could interfere with plaque formation or measures of gingivitis, in the period between Screening and the Baseline visit.

19. Periodontal Exclusions

a. A subject with signs of active periodontitis.
b. Subject with gingivitis which, in the opinion of the investigator, is not expected to respond to treatment with an over-the-counter dentifrice.
c. A subject who is receiving or has received treatment for periodontal disease (including surgery) within 12 months of Screening.

20. Dental Exclusions

a. A subject with active caries that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they were to participate in the study.
b. A subject with dentures (partial or full).
c. A subject with an orthodontic appliance (bands, appliances or fixed/ removable retainers).
d. A subject who has received orthodontic therapy within 12 months of Screening.
e. A subject with numerous restorations in a poor state of repair.
f. A subject with any dental condition (e.g. overcrowding) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they were to participate in the study.
g. A subject who has had dental prophylaxis within 12 weeks of Screening.
h. A subject who has had teeth bleaching within 12 weeks of Screening.
i. A subject with high levels of extrinsic stain or calculus deposits that might interfere with plaque assessments.

21. A subject who has previously been enrolled in this study.

22. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

Subjects will be stratified based on gender (male/ female), and baseline number of bleeding sites (low: <45 bleeding sites; high: ≥45 bleeding sites).

The stratification factor will give rise to 4 strata.

- Stratum 1: Male, Baseline number of bleeding sites <45.
- Stratum 2: Male, Baseline number of bleeding sites ≥45.
- Stratum 3: Female, Baseline number of bleeding sites <45.
- Stratum 4: Female, Baseline number of bleeding sites ≥45.

Subjects will be allocated to one of four strata and within each stratum, randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

5.5 Lifestyle Considerations

5.5.1 Dental Product/Treatment and Oral Hygiene Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit

- Subjects should not use any other oral care products (e.g. dentifrices, toothbrushes, mouthrinses) other than those provided during the study.
- Subjects should not carry out any interproximal dental cleaning. Use of dental floss, toothpicks, waterpicks or inter-dental brushes is prohibited (except for the removal of impacted food with non-antimicrobial products only).
- Subjects should delay any non-emergency dental treatment until after study completion (including dental prophylaxis).

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2) to Last Study Visit

- Subjects should refrain from oral hygiene procedures for 12 hours ((+6hr, -2hr) before their visit and attend the study site with overnight plaque growth.

5.5.2 Dietary and Smoking Restrictions

From Screening (Visit 1) to the Subject's Last Study Visit

- Subjects should not chew gum or consume any confectionery containing xylitol (e.g. mints).
- Subjects must abstain from smoking/ use of tobacco products (e.g. chewing tobacco, gutkha, pan containing tobacco, nicotine-based e-cigarettes).

Before Clinical Efficacy Assessment Visits: Baseline (Visit 2) to Last Study Visit

- Subjects must abstain from all food and drink (except water) for at least 4hrs prior to their scheduled assessment visits and until all assessments are complete during visit days. Water is permitted until 1 hour prior to their scheduled study visits.

5.5.3 Medication and Treatment Restrictions

The following medication and treatment restrictions apply for the duration of the study:

- If current/ concomitant medications/ treatments or traditional herbal ingredients/ treatments are used during the study, their identity, as well as their dosage and frequency, start and stop dates must be reported to the Investigator and recorded in the CRF.

For more information on concomitant medications, please refer to Section 6.8.

5.5.4 Contraception

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 5 days after the last dose of investigational product.

Female subjects of non-childbearing potential must meet at least one of the following criteria (subject-reported):

- Female who has achieved post-menopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;
- Female who has undergone a documented hysterectomy and/or bilateral oophorectomy;
- Female who has undergone one of the following procedures: bilateral tubal ligation or salpingectomy; hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion.

The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant

2. Intrauterine device (IUD) or intrauterine system
3. Combined estrogen and progestogen oral contraceptive
4. Injectable progestogen
5. Contraceptive vaginal ring
6. Percutaneous contraceptive patches
7. Male partner sterilization ≥3 months prior to taking part in the study, or documentation of a 0 sperm count/azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. An IUD must be in use at least 30 days prior to first study drug administration and barrier methods must be in use at least 14 days prior to study drug administration.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent, eligibility criteria, and any adverse events or incidents as applicable.)

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

Clinical examiners involved in screening and efficacy assessment procedures will be qualified dental professionals, registered to practice in Canada. Oral examinations to determine subject eligibility and all safety and efficacy (MGI, BI & TPI) assessments will be performed by an appropriately trained clinical examiner with a demonstrable recent history of use of these measures in clinical trials.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Investigational/Study Product Supplies

	Washout Product	Experimental Product	Positive control	Negative control
Product Name	Dentifrice containing 1000ppm fluoride as SMFP (Colgate Cavity Protection)	Experimental dentifrice containing 67% w/w sodium bicarbonate, 0.2% w/w sodium hyaluronate and 0.221% w/w sodium fluoride	Dentifrice containing 67% w/w sodium bicarbonate and 0.221% w/w sodium fluoride	Dentifrice containing 1100ppm fluoride as sodium fluoride (Crest Cavity Protection)
Product Master Formulation Code (MFC)	Canadian marketed product (NPN no. CCI)	CCI	CCI (NPN no. CCI)	Canadian marketed product (CCI)
Dose/ Application	Full ribbon of toothpaste to cover the head of toothbrush provided			
Route of Administration	Oral topical			
Usage Instructions	Subjects will brush their teeth for one timed minute twice a day (morning and evening)			
Return Requirements	All used/unused samples to be returned			

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Oral-B Sensi-soft manual toothbrush (Canadian market)	GSK CH	Individual toothbrush in commercial pack	One toothbrush at Screening for use with Lead-In product & one toothbrush at Baseline for use with assigned study dentifrice	Destroy at site using site disposal procedures	Return to 3rd party vendor
Countdown Timer	GSK CH	Individual timer in commercial pack	One timer at Screening visit	Subject to keep or destroyed at site using site disposal procedures	Return to 3rd party vendor
Pregnancy Test Kits (Canadian market)	GSK CH	Commercial pack	Not dispensed to subjects; only used at study site. Use as per study schedule	Destroy at site using site disposal procedures	Return to 3rd party vendor
Dosing Cups	GSK CH	Commercial pack	Not dispensed to subjects; only used at study site.	Destroy at site using site disposal procedures	Return to 3rd party vendor
Opaque bags	GSK CH	Commercial pack	Screening visit; Baseline visit; Visits 3, 4, 5 & 6 (Days 3, 7, 14 & 42 respectively)	Destroy at site using site disposal procedures	Return to 3rd party vendor
Chrom-O-Red plaque disclosing solution (Canadian marketed product)	Site	Commercial pack	Not dispensed to subjects; only used at study site. Use as per commercial label and study schedule	Destroy at site using site disposal procedures	Return to 3rd party vendor
Non-antimicrobial dental floss	Site	Commercial pack	Not dispensed to subjects; only used at study site. Use as per commercial label and study schedule	Destroy at site using site disposal procedures	Return to 3rd party vendor
Prophylaxis paste	Site	Commercial pack	Not dispensed to subjects; only used at study site. Use as per commercial label and study schedule	Destroy at site using site disposal procedures	Return to 3rd party vendor

For further information, please refer to the Global Clinical Supplies (GCS) Packaging and Labelling Proposal.

Detailed instructions for the disposal of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

The experimental and positive control dentifrices will be manufactured and filled into plain white tubes and supplied by GSK CH. The washout and negative control dentifrices will be sourced from the Canadian market.

All dentifrices will be presented to the clinical study site in tubes that have been overwrapped in white vinyl to obscure any branding on the commercial packs with a study label affixed. The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Global Clinical Supplies Department, GSK CH. Each subject will receive a sufficient number of tubes to cover usage during the treatment phase.

All sundry items will be supplied in their commercial packaging for dispensing by study staff as required.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

All products supplied are for use only in this clinical study and should not be used for any other purpose.

6.1.2 Preparation and Dispensing

Study products will be prepared and/or dispensed by qualified unblinded site personnel according to the dosage and administration instruction.

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

Study product will be dispensed by qualified unblinded site personnel per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of site staff should ensure the dispensing procedures are completed accurately. The investigational products will be dispensed in blinded fashion to the subject.

A record of product dispensing to each subject will be maintained in the dispensing log; completion of the dispensing procedure will be recorded in the case report form (CRF).

6.2 Administration

A record of the administration of the study products will be kept using a dispensing log and the CRF.

Subjects will be instructed to self-administer their investigational product according to the product use instructions provided to the subject. Subjects will receive a brushing instruction/diary sheet. This will outline the brushing instructions and will be used to record the date and time of each brushing occasion during the treatment period. Subjects will also be asked to note any missed brushings, and to use the diary to record any changes in medications, or new medications, or to diet. To ensure that subjects understand the dose of dentifrice to be used, staff will demonstrate what is meant by a 'full ribbon' (i.e. covering the length of the toothbrush head) and provide detailed oral hygiene instruction during the supervised toothbrushing in agreement with the study schedule and product usage instructions.

6.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such medication/dosing errors occurring to a study subject are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Medication/dosing errors are reportable irrespective of the presence of an associated AE, including:

- Medication/dosing errors involving subject exposure to any of the study products;
- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

Limited quantities of the study products will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Investigational/Study Product Storage

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Site staff will instruct subjects on the proper storage requirements for all take-home products.

6.4 Investigational/Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

Subjects will return used and unused tubes of the washout dentifrice to the investigator site at their Baseline visit (Visit 2). Subjects will return used and unused tubes of their assigned study dentifrice to the investigator site at their visits to the clinical study site as per the Schedule of Activities, with all study products returned at the end of the study (for most subjects this will be Visit 6). Study product return will be documented using the investigational/study product accountability form/record.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers), will be returned for destruction to GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

Return and destruction instructions for sundry items are provided in Table 6-2.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the study arms using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to the clinical study site. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

This study is described as examiner-blind (the subjects, investigator and clinical examiner(s) will be blinded to product received). The study statistician, other employees of the Sponsor (including the Clinical Research Scientist (CRS)) and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation.

To ensure the examiner remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use.

Subjects will be instructed not to remove study products from the opaque bags provided outside of the dispensing room, while at the study site. Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

Subjects will be stratified at the point of randomization based on their gender and number of bleeding sites (Low: < 45/High ≥ 45 bleeding sites) at baseline (see Section 4.1).

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required be required to inform the IRB/EC if the blind is broken.

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel.

A diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects will also use the diary to note any missed/ additional brushings, the reasons for any missed/ additional brushings, any issues with the dentifrice used, oral problems, illnesses, AEs, and any new medications/ treatments. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate. Subjects will also attend each study visit with all tubes of dentifrice provided (used and unused) for a visual check of product usage, and with their completed diary for review by study staff.

The number of any missed or additional applications or doses will be captured as protocol deviations and transcribed from the diary into the CRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

Supervised brushings will be carried out at the study site in agreement with the Schedule of Activities, to facilitate subject compliance with dosing and brushing instructions.

A threshold of compliance with allocated study treatment has been set as 80% of the recommended doses.

6.8 Concomitant Medication/Treatments

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication/treatments at each site visit.

Medication/treatments taken within 30 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after first treatment dose will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral

reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF.

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs) or Incidents.

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following: an oral examination.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

8.1 Screening: Visit 1

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will also be captured on the Informed Consent Form as this is the point at which all Adverse Events and Incidents will be captured from. The date and time of consent will be transcribed to the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

e-Consent is a tool that assists in the consent process by using multimedia components delivered by an electronic system (e.g. iPad/tablet). The multimedia components consist of video, audio, knowledge review, dictionary and electronic signature.

The site staff can use the system to consent the subject with the benefit of helping the subject understand the research they are taking part in and to control the consent process.

The system will allow for a copy of the consent to be printed and given to the subject and for consent documents to be retained by the site in PDF format.

A GSK CH approved vendor will be used to provide the system and training and help desk will be provided as needed.

If the country and/or site does not have approval to use the e-Consent system, or the subject does not want to use the e-Consent system, then the conventional paper process will be followed. It is possible to use the e-Consent system to educate the subject while using paper to obtain signatures.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race.

8.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history, including allergies or drug sensitivity, will be documented in the eCRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the eCRF.

8.1.4 Screening Procedures

The following procedures will be completed, and data recorded in the CRF:

- Informed consent.
- Demographics, medical history, prior/ current medications (including non-drug therapy), & smoking status.
- Oral soft tissue (OST) examination (Section 9.3.1)
- Oral hard tissue (OHT) examination (Section 9.3.2)
- Gross gingival assessment (Section 8.1.6)
- Female subjects of child-bearing potential *only* will complete a urine pregnancy test (UPT) (Section 9.1.2)
- Inclusion/exclusion criteria
- Subject eligibility
- Dispense washout products/ dentifrice, toothbrush, diary & timer.
- Oral hygiene instruction & supervised brushing with washout dentifrice.
- Adverse events & Incidents (Section 10)

8.1.5 Oral Examination/Assessment

Inclusion and exclusion criteria information will be documented in the eCRF. The following screening procedures should be carried out by a qualified dental professional:

- Oral soft tissue (OST) examination (as per Section 9.3.1).
- Oral hard tissue (OHT) examination (as per Section 9.3.2).
- Gross assessment of gingival health (as per Section 8.1.6) The oral examinations/assessments should be carried out as described in Section 9. All findings will be recorded in the eCRF.

8.1.6 Gross Assessment of Gingival Health

Visual assessment of gingival health will be performed by the clinical examiner to record the presence/absence of generalized mild-moderate plaque-induced gingivitis as per the inclusion criteria. (MGI/BI will not be recorded for this assessment).

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

8.1.7 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

8.1.8 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.9 Supervised Use of Washout Dentifrice

Eligible subjects will be provided with the washout dentifrice, toothbrush, diary and timer to use during the acclimatization period (2-4 weeks). Dentifrice usage instructions will be described to the subject and dosing of a full brush head with dentifrice will be demonstrated. Staff will supervise the subject carrying out first dosing/brushing with washout dentifrice and recording first use in their diary. Completion of all procedures will be documented in the CRF.

8.2 Study Period

8.2.1 Baseline: Day 0 (Visit 2)

Subjects will be admitted to the clinical study site 10-28 days after the Screening visit. The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the CRF:

- Return washout products/ compliance checks including diary review
- Review of current/ prior medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
- Urine pregnancy testing will be carried out on all female subjects of child bearing potential (Section 9.1.2)
- Full oral soft tissue (OST) examination (Section 9.3.1)
- Full oral hard tissue (OHT) examination (Section 9.3.2)
- MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
- BI assessment (Section 9.2.2)
- Plaque disclosure (Section 9.2.3)
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)

- Inclusion/exclusion criteria
- Subject eligibility
- Stratification/randomization
- Sub- & supra-gingival prophylaxis & flossing (Section 8.4)
- Plaque disclosure followed by first examiner and second clinician check with residual plaque removal, if applicable
- Confirmed plaque score of 0 following dental prophylaxis.
- Dispense study dentifrice, toothbrush, study instructions, diary & timer
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Supervised subject brushing at site
- Concomitant medications/ treatments will be collected as per Section 6.8.
- Adverse events & Incidents (Section 10)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

8.2.2 Day 3, Day 7, Day 14 (Visits 3-5)

The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the CRF:

- Collect study dentifrice, toothbrush & diary from subject
- Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
- Compliance checks including diary review
- Subject continuance
- Full OST examination (Section 9.3.1)
- MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
- BI assessment (Section 9.2.2)
- Plaque disclosure (Section 9.2.3)
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
- Return study dentifrice, toothbrush, study instructions and diary to subject
- Oral hygiene instruction review / compliance checks including diary completion review with subject
- Supervised subject brushing at site
- Adverse events & Incidents (Section 10)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.3 Day 42 (Visit 6)

The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the CRF:

- Collect study dentifrice, toothbrush, diary & timer (all study supplies) from subject
- Review of concomitant medications and non-drug treatments/ procedures, adverse events, incidents and lifestyle restrictions
- Compliance checks including diary review
- Subject continuance
- Oral soft tissue (OST) examination (Section 9.3.1)
- Oral hard tissue (OHT) examination (Section 9.3.2)
- MGI assessment (& repeatability assessment, where applicable) (Section 9.2.1)
- BI assessment (Section 9.2.2)
- Plaque disclosure (Section 9.2.3)
- TPI assessment (& repeatability assessment, where applicable) (Section 9.2.4)
- Complete optional second dental prophylaxis (as/ if deemed necessary by examiner) (Section 8.5)
- Adverse events & Incidents (Section 10)
- Study conclusion (Section 8.6)

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.3 Diary Review

The diary should be reviewed at every visit by the investigator, or suitably qualified designee, and the subject. Any subject comment captured in the diary which is considered an adverse event or Incident will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in Adverse Event and Serious Adverse Events. Incident reporting procedures are summarized in Definition of and Procedure for Reporting Medical Device Incidents (Section 10.9).

Any additional comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject and entered into the CRF as appropriate.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log.

8.4 Dental Prophylaxis

A suitably qualified member of clinical staff (e.g. a dentist or hygienist) will provide professional dental prophylaxis for each randomized subject (using conventional prophylaxis paste and periodontal instruments as required), followed by flossing, to remove sub- and supra-gingival calculus, stain, plaque and debris from the teeth. A second clinician will confirm all sub- and supra-gingival calculus, visible stain, plaque and debris has been removed (visually, and by tactile examination using a dental explorer). If necessary, additional dental cleaning will be carried out to achieve this. Prophylaxis may be carried out by different clinicians to facilitate subject flow.

Following prophylaxis, it should be confirmed that the subject whole mouth post-prophylaxis TPI = 0. Completion of this procedure should be recorded in the eCRF.

In addition, at the final study visit, subjects will be offered a dental prophylaxis if determined appropriate in the opinion of the investigator or suitably clinically qualified designee as detailed in Section 8.5.

8.5 End of Study Optional Prophylaxis

Subjects who, in the opinion of the clinical examiner, would benefit from dental prophylaxis following their participation in the study will be offered full mouth dental prophylaxis (using conventional prophylaxis paste and periodontal instruments as required) on completion of all clinical assessments. Prophylaxis may be carried out by different, appropriately qualified clinicians to facilitate subject flow.

8.6 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.7 Follow-up Visit/ Phone Call

The study site may contact a subject to follow up an AE or Incident post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances,

outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol. A single examiner will be responsible for the conduct of the clinical measures of gingivitis/ plaque accumulation for the duration of the study.

Eligible tooth assessments will be accomplished by oral examination and will evaluate dentition exclusions along with a gross gingival assessment in relation to the general dentition inclusion/ exclusion criteria. Assessments will be carried out by the investigator, or qualified designee, against the inclusion/ exclusion criteria. Ineligible subjects will not be re-screened.

9.1.1 Gross Assessment of Gingival Health

Visual assessment of gingival health will be performed to record the presence/absence of generalized mild-moderate plaque-induced gingivitis as per the inclusion criteria. (MGI/BI will not be recorded for this assessment).

Findings from this examination performed at the Screening Visit will be used to determine subject eligibility.

9.1.2 Urine Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at Screening (Visit 1) and Baseline (Visit 2). Results will be obtained prior to dosing during each visit.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol

The same examiner will be used throughout the study for each clinical index to eliminate the possibility of inter-examiner variability.

9.2.1 Modified Gingival Index (MGI) Assessment (CCI [redacted])

The MGI assessment is a non-invasive evaluation which focuses on the visual symptoms of gingivitis (for example, redness, texture, edema). The MGI will be assessed on the facial and lingual surfaces of each scorable tooth (second permanent molar to second permanent molar in each arch) by an appropriately qualified examiner. Two scores will be recorded buccally/labially (papilla and margin) and two scores lingually/palatally (papilla and margin). The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

The MGI scoring system will be as follows:

Table 9-1 Modified Gingival Index scoring system

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in colour; little change in texture of any portion of the marginal or papillary gingival unit
2	Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit
3	Moderate inflammation; glazing, redness, edema, and/ or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation; marked redness, edema and/ or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

The MGI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

9.2.2 Bleeding Index (BI) Assessment (CCI [redacted])

The BI assesses the number of bleeding points elicited on probing as a measure of gingival condition. The gingivae will be air dried and then the examiner will use an Oulix color coded periodontal PCPII 5B Hu-Freidy or blunt-ended CPI probe to assess bleeding. The probe will be gently inserted into the gingival crevice to a depth of approximately 1 millimeter (mm) and then run around the tooth (at angle of ~ 60° to the long axis of the tooth), gently stretching the epithelium while sweeping from interproximal to interproximal along the sulcular epithelium. Minimum force should be used to avoid damage to the gingival tissue. The BI will be assessed on the facial and lingual gingival surfaces of each scorable tooth (7-7 in each arch). Three scores (according to the scale below) should be recorded buccally/labially (distal, body, mesial sites) and three scores lingually/palatally. All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed.

The BI scoring system will be as follows:

Table 9-2 Bleeding Index scoring system

Score	Description
0	No bleeding after 30 seconds
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

The BI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

Repeatability exercise will not be performed for BI.

9.2.3 Plaque Disclosure

Dental plaque is colorless and so is usually disclosed ('stained') prior to assessment. The disclosing solution will be used according to the manufacturer's instructions.

- At the request of the subject, the clinician may apply a thin layer of petroleum jelly to the subject's lips, as a barrier to help minimize staining by the disclosing solution. Care should be taken to ensure no petroleum jelly comes into contact with the labial surfaces of the anterior teeth as this could impact clinical assessments in this region.
- The subject will rinse their mouth with 10 mL tap water for 10 seconds to remove any food debris and expectorate.
- The clinician will then apply the plaque disclosing solution as per the label instructions. Care will be taken not to dislodge the plaque during this process. The subject will then rinse with 10 mL tap water for 10 seconds and expectorate to remove excess solution.

Plaque may be redisclosed between the TPI and repeat assessments at the discretion of the clinical examiner.

9.2.4 Plaque Index (TPI) Assessment (CCI [redacted])

The Turesky Modification of the Quigley Hein Plaque Index (CCI [redacted]) will be used to assess plaque on all gradable teeth meeting the inclusion/ exclusion criteria, and will be performed by an appropriately qualified examiner. Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed.

The plaque will first be disclosed using a plaque disclosing dye solution, in agreement with the manufacturer's instructions. The TPI will be assessed on the facial and lingual surfaces of each scorable tooth. (7-7 in each arch). Three scores should be recorded bucally/ labially (distal, body, mesial sites) and three scores lingually/ palatally (distal, body, mesial sites).

Disclosed plaque will be scored as follows:

Table 9-3 Turesky Plaque Index Scoring System

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface

The TPI will be assessed by the same examiner on all evaluable teeth from Baseline onwards as indicated in the Schedule of Activities.

9.2.1 Repeatability Assessments

The clinical examiner selected for this study will have demonstrated their ability to replicate their own scores (intra-examiner repeatability) on a tooth site-by-tooth site basis in previous studies and/or calibration exercises. Repeat MGI and TPI assessments will be performed by the clinical examiner at Visits 2 - 6. At least 2 repeat assessments should be performed for each index on each clinical assessment day (≥1 in the morning; ≥1 in the afternoon). 'Repeat' subjects will be selected at random from those in attendance. Different subjects can be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes between original and repeat assessments for a given subject and ideally separated by another subject. No other procedure on the subject should be carried out between the first and the repeat assessment. Where possible, the clinical examiner should assess a different subject in the intervening period.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.3.1 Oral Soft Tissue Examination (OST)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee. The OST examination will be accomplished throughout the study by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands.

The results of the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities. Any post-treatment soft tissue abnormality, or worsening of a pre-existing condition, observed by the examiner or reported by the subject will be recorded on the CRF. Any abnormalities or worsening of a pre-existing condition observed by the clinical

examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

During the oral examination, if any abnormalities on the oral soft tissues are detected, the subject will be advised to seek further medical/ dental advice from their dentist or general medical practitioner as deemed appropriate in the opinion of the clinical examiner.

9.3.2 Oral Hard Tissue (OHT) Assessment

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. Subjects with evidence of gross intra-oral neglect or the need for extensive dental therapy will be excluded.

The OHT examination will assess grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification, faulty restorations and implants. The examination will be performed by direct observation.

During the oral examination, if any abnormalities on the oral hard tissues are detected, the subject will be advised to seek further medical/ dental advice from their dentist or general medical practitioner.

Observations will be listed as "Absent" or "Present" and conditions noted as present will be described. Examination findings will be described and documented in the CRF. Any abnormalities or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening will be recorded as an AE.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations:**
    - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

All AEs, and therefore all SAEs will be collected immediately after a subject consents to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The investigator or medically qualified designee will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change his/her opinion of

causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD). The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD).

The investigator will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.7.1 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box (PPD within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD). Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD). Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will discontinue study treatment and/or be withdrawn from the study.

10.9 Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the toothbrushes and urine pregnancy test kits.

10.9.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE

(serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The GSK CH Study Manager should be notified of the situation by telephone or email.

Email the Incident Report Forms to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox PPD, responsible for the study and other GSK CH personnel as appropriate.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

The investigator will follow the following directions regarding the reporting of a device failure (malfunction):

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.

10.9.3 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.9.4 Regulatory and Ethics Reporting Requirements for Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified. The CRF and/or diary can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party BDM Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, GSKDrug.

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data will be collected from a diary, questionnaire, or other specified document, etc. and entered into the data management system (DMS).

Electronic Patient reported outcome (ePRO) data may be collected using electronic devices and transferred electronically to GSKCH or Third-party DM vendor. ePRO will not be used for this study.

All PRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as required.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or Third-Party Vendor.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES.

12.1 Sample Size Determination

No formal study powering was conducted. Forty (40) randomized subjects per treatment group are deemed to be sufficient for generating sufficient efficacy and safety data to evaluate the combination product (sodium bicarbonate and sodium hyaluronate), with sodium bicarbonate dentifrice and regular fluoride dentifrice in this PoP study.

Sufficient subjects will be screened (approximately 160) by the study site so that at least 120 subjects (approximately 40 per treatment group) who fulfill all the entry criteria will be randomized, which should ensure that approximately 36 evaluable subjects per group complete the week 6 assessment (thus allowing for a 10% drop-out rate).

12.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalization of the protocol and prior to study unblinding.

12.2.1 Definition of Analysis Populations

The Safety population will include all randomized subjects who receive at least one dose of study product. This population will be based on the product the subject received.

The modified Intent-To-Treat (mITT) population will include all randomized subjects who receive at least one dose of study product and have at least one post baseline (post treatment) efficacy measurement. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.

The Per Protocol (PP) population includes all mITT subjects who fully comply with all study procedures and restrictions. Violations excluding from PP population will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.

The repeatability population for MGI is defined as all subjects who have at least one repeat MGI clinical assessment at any visit.

The repeatability population for TPI is defined as all subjects who have at least one repeat TPI clinical assessment at any visit.

12.2.2 Exclusion of Data from Analysis

Protocol violations considered to have had affected efficacy will lead to exclusion of either subject or data from PP analyses. Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

A PP analysis will be performed only if 10% or more mITT subjects are excluded from PP population. A decision on whether a PP analysis will be performed will be made prior to study unblinding.

12.2.3 Demographic and Baseline Characteristics

Age and other continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum and maximum. Gender, race and other categorical variables will be summarized using frequency counts and percentages for the safety and mITT populations.

Medical history and current medical conditions will be listed.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

Compliance with study product use (based on number of brushings) will be summarized and listed for the mITT population.

Compliance is defined as: Compliance (%) = Actual Number of brushings / Expected Number of brushings ×100.

A threshold of compliance with allocated study treatment has been set as 80% of the recommended doses. Subjects with overall compliance <80% will be considered protocol deviations and assessed at the time of Blinded Data Review for exclusion from the Per Protocol (PP) population.

12.2.4.2 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during treatment will be listed for all randomized subjects.

12.2.5 Primary Analysis(es)

Number of bleeding sites at 6 weeks

The primary time point is week 6 and primary comparison will be between the 67% w/w sodium bicarbonate & 0.2% w/w HMW sodium hyaluronate and the fluoride control dentifrice. As there is only a single primary objective no adjustment for multiple comparisons is required.

These analyses will be conducted on the mITT population.

The primary efficacy variable is the number of bleeding sites and will be derived from the bleeding index, whereby a site will be considered bleeding if the bleeding index score is 1 or 2 and will be considered not bleeding if the bleeding index score is 0.

Summary statistics including mean, standard deviation (SD), standard error (SE), median, minimum, maximum will be provided by visit and randomized treatment group. Raw means and SE will also be plotted over time by treatment group.

The number of bleeding sites at 6 weeks will be analyzed using an ANCOVA model with treatment group and gender as factors and baseline number of bleeding sites as covariate. Note that since the baseline number of bleeding sites will be included as a covariate, the number of bleeding sites stratification value will not be included in the model.

Using the above model, adjusted means, along with 95% CIs will be reported by treatment group. Treatment difference between the 67% w/w sodium bicarbonate & 0.2% w/w HMW sodium hyaluronate and the fluoride control dentifrice will also be provided along with 95% confidence intervals.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (such as van Elteren test adjusting for gender and baseline number of bleeding sites stratification) will be used.

12.2.6 Secondary Analysis(es)

Number of bleeding sites at 6 weeks

Using the same methodology as described above for primary analyses, pairwise treatment differences will be provided along with 95% confidence intervals for the following treatment comparisons:

- 67% w/w sodium bicarbonate & 0.2% w/w HMW sodium hyaluronate vs. 67% w/w sodium bicarbonate
- 67% w/w sodium bicarbonate vs. fluoride control

These analyses will be conducted on the mITT population.

12.2.7 Safety Analyses

All assessments of safety will be based on the safety population. Safety analyses will be performed according to the treatment that the subject received and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be collected immediately after a subject provides consent to participate in the study by the completion of the informed consent form. AEs will be regarded as treatment emergent if they occur on or after the first treatment application.

Treatment Emergent Adverse Events (by SOC/PT), Treatment Emergent Adverse Events (Oral/Non-Oral), Related Treatment Emergent AEs will be summarized by treatment.

Deaths, Non-fatal Serious Adverse Events, Treatment Emergent Adverse Events leading to study or drug discontinuation, Treatment Emergent Adverse Events Classified as oral, and incidents will be listed. The results of the OST and OHT examinations will be listed.

12.2.8 Exploratory Analyses

All the exploratory analyses described below will be conducted on the mITT population.

Number of bleeding sites at 3 days, 1 week, 2 weeks

The number of bleeding sites at 3 days, 1 and 2 weeks will be analyzed using same methodology as the primary efficacy variable described above.

Mean Bleeding index (BI) at 3 days, 1, 2 and 6 weeks

In addition to the primary analysis based on the number of bleeding sites, an analysis of gingival bleeding will be performed on the full bleeding index. The mean bleeding index will be calculated taking the average over all tooth sites for a subject.

Summary statistics including mean, SD, SE, median, minimum, maximum will be provided by visit and randomized treatment group. Raw means and SE will also be plotted over time by treatment group.

Mean BI will be analyzed using ANCOVA model with treatment group and gender and number of bleeding sites strata as factors, and baseline BI score as covariate. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (such as van Elteren test adjusting for gender and baseline number of bleeding sites stratification) will be used.

Mean Modified Gingival index (MGI) at 3 days, 1, 2 and 6 weeks

Mean MGI will be calculated taking the average over all tooth sites for a subject.

Summary statistics including mean, SD, SE, median, minimum, maximum will be provided by visit and randomized treatment group. Raw means and SE will also be plotted over time by treatment group.

Mean MGI score will be analyzed using ANCOVA model with treatment group, gender and number of bleeding sites strata as factors and baseline MGI score as covariate. Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (such as van Elteren test adjusting for gender and baseline number of bleeding sites stratification) will be used.

Mean Plaque index (TPI) (overall and interproximal) at 3 days, 1, 2 and 6 weeks

Mean overall plaque will be calculated taking the average over all tooth sites for a subject.

The interproximal plaque score will be calculated in the same way as for the overall scores but just based on the mesiofacial, distofacial, mesiolingual and distolingual surfaces.

Summary statistics including mean, SD, SE, median, minimum, maximum will be provided by visit and randomized treatment group for overall plaque and interproximal plaque. Raw means and SE will also be plotted over time by treatment group.

Overall plaque score and interproximal plaque score will be analyzed using ANCOVA model with treatment group, gender and number of bleeding sites strata as factors and baseline plaque score as covariate.

Adjusted means for all treatments and all pairwise treatment differences will be provided along with 95% confidence intervals.

The assumption of residual normality and variance homogeneity in ANCOVA analysis will be investigated through residual plots. If violated, data transformation or a nonparametric method (such as van Elteren test adjusting for gender and baseline number of bleeding sites stratification) will be used.

Subgroups analyses – Mean MGI and Mean BI at 3 days, 1, 2 and 6 weeks

A subgroup analysis to evaluate and compare mean MGI and number of bleeding sites in low (<45) and high (≥45) bleeding sites groups will be conducted using the same methodology as described above for each respective endpoint.

12.2.9 Other Analyses

Repeatability of the examiner

The repeatability of the examiner in conducting the MGI and TPI assessments will also be performed. The repeat plaque and MGI assessments will be compared to the original assessments. The repeat assessment is not to be used in any efficacy analysis. The first and second assessments will be cross tabulated.

A weighted Kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis. Reliability will be deemed

- Excellent if $\kappa > 0.75$
- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

This analysis will be conducted on each respective index repeatability population (MGI population and TPI population).

12.2.10 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data.

12.2.11 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK CH requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK CH or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. A member of clinical study site personnel not involved in providing subject care, or conduct of any of the dental assessments will be responsible for obtaining written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH-sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

GSK intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually-agreeable location.

GSK CH will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of the investigational product at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

14 REFERENCES

Available on request

CCI [redacted].

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

15 APPENDICIES

15.1 Product Usage Instructions

INSTRUCTIONS

Brush twice a day (morning and evening) for 1 timed minute.

Each time you brush:

- Dispense a ribbon of toothpaste covering the entire length of the toothbrush head (see picture below).
- Set your timer for 1 minute, and then brush all the teeth in your mouth in your usual manner for 1 timed minute.
- Please record each brushing in the diary. Note any changes to these brushing procedures and reasons for changes (e.g. missed brushings, extra brushings).
- On the day before your next visit, please **record the actual time of your last brushing before attending site**. Please remember do not brush your teeth within 12 hours (+6 hours, -2 hours) before your scheduled study assessment visits.
- Please record any changes to your health, medications (prescription and over the counter medications) or treatments in the diary.
- Please bring your diary card (completed and not completed), toothpaste and toothbrush to the next study visit.
- Please do not remove or deface any part of the study label.

Please do not share your study toothpaste with anybody and do not discuss with the examiner your experience with your assigned toothpaste (e.g. taste, color or smell).

15.2 ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BDM	Biostatistics and Data Management
BDS	Bachelor of Dental Surgery
BI	Bleeding index
CI	confidence interval
CRF	case report form
CRS	Clinical Research Scientist
CSR	Clinical study report
Da	Dalton
DMS	Data management system
EC	ethics committee
ECG	echocardiogram
EDC	Electronic data capture
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSFV	First subject first visit
FSH	Follicle-stimulating hormone
GCF	Gingival crevicular fluid
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
HA	hyaluronic acid (sodium hyaluronate)
HMW	High molecular weight
hrs	hours
IB	investigator's brochure
ICH	International Conference on Harmonisation
IND	investigational new drug application
IRB	institutional review board
ITT	Intent to treat
IUD	intrauterine device
LLC	limited liability company
MedDRA	medical Dictionary for Regulatory Activities
MFC	Master formulation code
MGI	Modified gingival index
mm	Millimeter
MW	Molecular weight

Abbreviation	Term
N/A	not applicable
No.	Number
NJ	New Jersey
NNHP	Non-prescription Natural Health Product
OHT	Oral hard tissue
OST	Oral soft tissue
PI	principal investigator
PII	Personally identifiable information
PoP	Proof-of-principle
PP	Per protocol
PRO	Patient reported outcome
RAP	Reporting and analysis plan
SAE	serious adverse event
SD	Standard deviation
SE	Standard error
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
SUSAR	Suspected unexpected serious adverse reaction
TPI	Turesky modification of the Quigley Hein Plaque Index
UK	United Kingdom
UPT	Urine pregnancy test
US	United States
w/w	Weight for weight